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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CIMA
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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/661,693	PATHER ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,25-27,30-33,83,86,88,91,93,94 and 105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,25-27,30-33,83,86,88,91,93,94 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/12/2007 has been entered.

The examiner notes the receipt of the amendments and remarks received in the office on 9/12/2007 amending claims 22, 30, 31, 33 and 100 and canceling claim 26. Claims 22, 25-27, 30-33, 83, 86, 88, 91, 93, 94 and 105 are pending and are being examined on the merits herein.

Response to Remarks

The rejection of claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 11/026,327 ('327) is withdrawn due to the abandonment of the co-pending application. Applicants' arguments regarding the rejection of claims 22, 26, 27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 under 35 U.S.C. 103(a) as being unpatentable over McCarty in view of Wehling et al and further in view of Streisand et al. have been fully considered and found not persuasive. Applicants' arguments regarding the rejection of claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. in view of Wehling et al. and further in view of Streisand

et al have been fully considered and found not persuasive. Hence the rejections are being maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 11/026,132 ('132)

The instant application teaches a tablet comprising fentanyl, at least one pH adjusting substance and saliva activated effervescent couple and the co-pending application '132 teaches a tablet comprising fentanyl, effervescent couple and pH adjusting substance.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention overlaps with that previously claimed. Thus, the copending application is directed to fentanyl, an effervescent dosage form, which anticipates the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 11/027,353 ('353).

The instant application teaches a tablet comprising fentanyl, at least one pH adjusting substance and saliva activated effervescent couple and the co-pending application '353 teaches a dosage form comprising fentanyl, an effervescent couple and pH adjusting substance.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention overlaps with that previously claimed. Thus, the copending application is directed to fentanyl, an effervescent dosage form, which anticipates the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 29-33 of copending Application No. 11, 511, 098 ('098).

The instant application teaches a tablet comprising fentanyl, at least one pH adjusting substance and saliva activated effervescent couple and the co-pending

application '098 teaches a tablet comprising fentanyl, an effervescent couple and pH adjusting substance.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention overlaps with that of the co-pending application. The copending application is directed to fentanyl tablet, an effervescent dosage form, which anticipates the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 22, 30, 33, 91, 93, 94, 105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 15 of copending Application No. 11, 521, 796 ('796).

The instant application teaches a tablet comprising fentanyl, at least one pH adjusting substance, disintegrant and saliva activated effervescent couple and the co-pending application '098 teaches a tablet comprising fentanyl, an effervescent couple, disintegrant and pH adjusting substance.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention overlaps with that of the co-pending application. The copending application is directed to fentanyl, an effervescent dosage form, which anticipates the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22, 26, 27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCarty (US 5,073,374) in view of Wehling et al. (WO 91104757) and further in view of Streisand et al. (Buccal absorption of fentanyl is pH-dependent in dogs', Anesthesiology, (1995 Mar), 82 (3), pp. 759-64).

McCarty teaches fast dissolving buccal tablets particularly useful for the administration of active ingredients that show poor bioavailability upon administration through non-parenteral modes (See Abstract). Such active ingredients include analgesics such as fentanyl (col. 1, lines 14-30). The tablets of McCarty are placed in the buccal pouch of the oral cavity and allowed to dissolve (col. 4, lines 3-7).

McCarty does not teach the effervescent couple of the instant claims.

Wehling et al. teach effervescent dosage forms for direct oral administration (i.e. for direct insertion into the mouth of a patient), which comprise at least one systemically distributable ingredient (e.g. a drug), 5 to about 50 % effervescent disintegration agents (a soluble acid source and a carbonate source) and adjuvants such as binders, flavors, colors, fillers, non-effervescent disintegrants, etc. (p. 3, lines 30-37; p. 11, lines 22-38; p. 12, lines 1-19; p 13, lines 3-12, p. 14, lines 25-37; p. 15). The reference further

teaches that in preferred embodiments the effervescent disintegration agent may include, without limitation, at least one acid selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one base selected from the group consisting of carbonate salts, bicarbonate salts and mixtures thereof (p 6, lines 7-14, p 12, lines 2-19). The reference teaches that carbonate sources include sodium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate etc (p 12, lines 13-19). "This may be useful to enhance taste and/or performance of a tablet containing an overage of either component" (p. 12, lines 36-38). Analgesics are among the drugs that can be administered in oral effervescent dosage forms of Wehling et al. (p. 9, line 29). The amount of the non-effervescent disintegration agents such as corn starch, potato starch, alginates may comprise up to about 20 % by weight, and the amount of either acid or carbonate source may exceed the amount of the other component (p. 12, lines 20-36; p. 15, lines 3-8). The tablets of Wehling et al. dissolve in the mouth in between about 30 seconds and about 7 minutes (p. 13, lines 13-24). Wehling et al. teach that the use of the effervescent disintegration agents provides the following benefits: masking the objectionable flavor of medicaments, facilitating the disintegration of the tablet and providing pleasant organoleptic sensation (p. 6, lines 15-26). The reference teach that the effervescence disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide distinct sensation of effervescence when the tablet is placed in the mouth of a patient (p 4. lines 4-8).

Further, such dosage forms are particularly useful in administration of medications to patients who cannot or will not chew, such as children and the elderly (p. 4, lines 9-25).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the fast dissolving buccal fentanyl tablets of McCarty such that to employ effervescent disintegration agents. One having ordinary skill in the art would have been motivated to do this to obtain even faster dissolution as well as masking the objectionable flavor of medicaments and providing pleasant organoleptic sensation, to provide dosage forms that are useful in administration of medications to individuals who cannot or will not chew, such as debilitated patients, patients who have difficulty swallowing solids, and the elderly as suggested by Wehling et al. Further, while suggesting that the amount of either acid or carbonate source may exceed the amount of the other component in order to enhance taste and/or performance of a tablet containing an overage of either component, the Wehling reference does not explicitly teach the at least one pH adjusting substance which is a base as claimed herein.

Streisand et al. teach that the buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic, which is due to an increase in the fraction of unionized fentanyl (Abstract; Discussion). The reference further teaches that fentanyl citrate is a weak base, it may be possible to speed absorption by increasing the pH of the delivery vehicle, thus converting more fentanyl to the unionized form and in theory unionized drugs pass through biologic membranes more easily than ionized drugs (p 760, lines 2-9). The

reference teaches the administration of fentanyl citrate to dogs through the buccal mucosa (p 760, col.2, lines 9-10).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of Wehling et al. such as to employ the excess of the carbonate source (base). One having ordinary skill in the art would have been motivated to do this to obtain basic pH as which the buccal absorption, bioavailability and permeability of fentanyl increase, thus making the tablet more effective, as suggested by Streisand et al. With respect to Claims 93 and 94, which recite tablet "adapted for" gingival and sublingual administration, respectively, these types of administration are obvious variations of oral transmucosal administration. Therefore, Claims 93 and 94 don't recite any additional ingredients and/or characteristics; therefore, the combination of references discussed above meets the claimed limitations.

Claims 22, 26, 27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wehling et al. (WO 91104757) in view of McCarty (US 5,073,374) and further in view of Streisand et al. (Buccal absorption of fentanyl is pH-dependent in dogs', Anesthesiology, (1995 Mar), 82 (3), pp. 759-64).

Wehling et al's teachings discussed as above.

The reference does not explicitly teach fentanlyl to be the analgesic drug in the effervescent dosage form.

Wehling's teachings discussed as above.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to add fentanyl an analgesic to the effervescent dosage form of Wehling. One of ordinary skill in the art would have been motivated to do so because McCarty teach fentanyl as an analgesic and in the buccal formulation and Wehling teach effervescent dosage forms comprising analgesic that provide faster dissolution and provide medication forms to individuals who cannot or will not chew, such as debilitated patients, patients who have difficulty swallowing solids, and the elderly.

Wehling reference or McCarty does not explicitly teach the at least one pH adjusting substance which is a base as claimed herein.

Streisand et al. teachings discussed as above.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of Wehling et al. such as to employ the excess of the carbonate source (base). One having ordinary skill in the art would have been motivated to do this to obtain basic pH as which the buccal absorption, bioavailability and permeability of fentanyl increase, thus making the tablet more effective, as suggested by Streisand et al. With respect to Claims 93 and 94, which recite tablet "adapted for" gingival and sublingual administration, respectively, these types of administration are obvious variations of oral transmucosal administration. Therefore, Claims 93 and 94 don't recite any additional ingredients and/or characteristics; therefore, the combination of references discussed above meets the claimed limitations.

Claims 22, 26, 27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Streisand (Anesthesiology, 1991, 75(2), 223-9) in view of Streisand et al. (Buccal absorption of fentanyl is pH-dependent in dogs', Anesthesiology, (1995 Mar), 82 (3), pp. 759-64) and further in view of Wehling et al. (WO 91104757).

Streisand teach oral transmucosyl fentanyl citrate as a noninvasive dosage form of fentanyl to provide children and adults with sedation, anxiolysis and analgesia. The reference further teaches that systemic bioavailability of oral transmucosyl fentanyl was greater than the oral solution.

Streisand (1991) does not teach at least one pH adjusting substance.

Streisand et al. (1995) teach that oral and nasal mucosa has emerged as sites for the administration of potent analgesics including fentanyl (p 759, col. 2, lines 1-2). The reference further teach that the buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic, which is due to an increase in the fraction of unionized fentanyl (Abstract; Discussion). The reference teaches that fentanyl citrate is a weak base, it may be possible to speed absorption by increasing the pH of the delivery vehicle, thus converting more fentanyl to the unionized form and in theory unionized drugs pass through biologic membranes more easily than ionized drugs (p 760, lines 2-9). The reference teaches the administration of fentanyl citrate to dogs through the buccal mucosa (p 760, col.2, lines 9-10). The reference teaches the addition of phosphate buffer to dry fentanyl citrate to obtain fentanyl solutions of pH 6.6, 7.2 and 7.7 (p 760,

col.2, lines 9-12). The reference further teaches that fentanyl can be absorbed through the oral mucosa more rapidly and to a greater extent by increasing the pH of the delivery solution applied to the oral mucosa.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of Streisand (1991) such as to add a pH buffer, phosphate buffer solution to fentanyl citrate to obtain fentanyl solutions of pH 6.6, 7.2 and 7.7. One of ordinary skill in the art would have been motivated to do so because Streisand et al. (1995) teach that fentanyl can be absorbed through the oral mucosa more rapidly and to a greater extent by increasing the pH of the delivery solution applied to the oral mucosa. One having ordinary skill in the art would have been motivated to do this to obtain basic pH as which the buccal absorption, bioavailability and permeability of fentanyl increase, thus making the tablet more effective, as suggested by Streisand et al. (1995).

The references do not teach effervescent couple of the instant claims.

Wehling et al. teach effervescent dosage forms for direct oral administration (i.e. for direct insertion into the mouth of a patient), which comprise at least one systemically distributable ingredient (e.g. a drug), 5 to about 50 % effervescent disintegration agents (a soluble acid source and a carbonate source) and adjuvants such as binders, flavors, colors, fillers, non-effervescent disintegrants, etc. (p. 3, lines 30-37; p. 11, lines 22-38; p. 12, lines 1-19; p 13, lines 3-12, p. 14, lines 25-37; p. 15). The reference further teaches that in preferred embodiments the effervescent disintegration agent may include, without limitation, at least one acid selected from the group consisting of citric

acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one base selected from the group consisting of carbonate salts, bicarbonate salts and mixtures thereof (p 6, lines 7-14, p 12, lines 2-19). The reference teaches that carbonate sources include sodium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate etc (p 12, lines 13-19). "This may be useful to enhance taste and/or performance of a tablet containing an overage of either component" (p. 12, lines 36-38). Analgesics are among the drugs that can be administered in oral effervescent dosage forms of Wehling et al. (p. 9, line 29). The amount of the non-effervescent disintegration agents such as corn starch, potato starch, alginates may comprise up to about 20 % by weight, and the amount of either acid or carbonate source may exceed the amount of the other component (p. 12, lines 20-36; p. 15, lines 3-8). The tablets of Wehling et al. dissolve in the mouth in between about 30 seconds and about 7 minutes (p. 13, lines 13-24). Wehling et al. teach that the use of the effervescent disintegration agents provides the following benefits: masking the objectionable flavor of medicaments, facilitating the disintegration of the tablet and providing pleasant organoleptic sensation (p. 6, lines 15-26). The reference teach that the effervescence disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide distinct sensation of effervescence when the tablet is placed in the mouth of a patient (p 4. lines 4-8). Further, such dosage forms are particularly useful in administration of medications to patients who cannot or will not chew, such as children and the elderly (p. 4, lines 9-25).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify oral transmucosyl fentanyl citrate dosage forms such that to employ effervescent disintegration agents. One having ordinary skill in the art would have been motivated to do this to obtain even faster dissolution as well as masking the objectionable flavor of medicaments and providing pleasant organoleptic sensation and as a useful medication to patients who cannot or will not chew, such as children and the elderly as suggested by Wehling et al. Wehling et al. suggest that the amount of either acid or carbonate source may exceed the amount of the other component in order to enhance taste and/or performance of a tablet containing an overage of either component. With respect to Claims 93 and 94, which recite tablet "adapted for" gingival and sublingual administration, respectively, these types of administration are obvious variations of oral transmucosal administration. Therefore, Claims 93 and 94 don't recite any additional ingredients and/or characteristics; therefore, the combination of references discussed above meets the claimed limitations.

Claims 22, 26, 27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norling et al (U.S. 5,958458) in view of Wehling et al. (WO 91104757).

Norling et al. teach pharmaceutical formulations comprising a pharmaceutically inert carrier such as magnesium carbonate, an active substance that includes an analgesic such as fentanyl (see Abstract, col. 6, line 23). The reference teaches the formulation for oral dosage form includes effervescent tablets (col. 13, lines 29-30) and

teaches citric acid (32 % by weight), sodium hydrogen carbonate (32 % by weight) for effervescent reactions (col. 17, lines 6-10, example 13). The reference also teach the addition of disintegrating agents, for example, cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid in the oral dosage formulation (col. 13, lines 47-50). The reference teaches buccal administration of the formulation (col. 40, claim 13). The herein claimed property of pH adjusting is inherent of the compound magnesium carbonate and will act as a pH adjusting agent in the formulation.

The reference does not teach the weight percent of disintegration agent.

Wehling et al. teach effervescent dosage forms for direct oral administration (i.e. for direct insertion into the mouth of a patient), which comprise at least one systemically distributable ingredient (e.g. a drug), 5 to about 50 % effervescent disintegration agents (a soluble acid source and a carbonate source) and adjuvants such as binders, flavors, colors, fillers, non-effervescent disintegrants, etc. (p. 3, lines 30-37; p. 11, lines 22-38; p. 12, lines 1-19; p 13, lines 3-12, p. 14, lines 25-37; p. 15). The reference further teaches that in preferred embodiments the effervescent disintegration agent may include, without limitation, at least one acid selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one base selected from the group consisting of carbonate salts, bicarbonate salts and mixtures thereof (p 6, lines 7-14, p 12, lines 2-19). The reference teaches that carbonate sources include sodium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate etc (p 12,

lines 13-19). "This may be useful to enhance taste and/or performance of a tablet containing an overage of either component" (p. 12, lines 36-38). Analgesics are among the drugs that can be administered in oral effervescent dosage forms of Wehling et al. (p. 9, line 29). The amount of the non-effervescent disintegration agents such as corn starch, potato starch, alginates may comprise up to about 20 % by weight, and the amount of either acid or carbonate source may exceed the amount of the other component (p. 12, lines 20-36; p. 15, lines 3-8). The tablets of Wehling et al. dissolve in the mouth in between about 30 seconds and about 7 minutes (p. 13, lines 13-24). Wehling et al. teach that the use of the effervescent disintegration agents provides the following benefits: masking the objectionable flavor of medicaments, facilitating the disintegration of the tablet and providing pleasant organoleptic sensation (p. 6, lines 15-26). The reference teach that the effervescence disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide distinct sensation of effervescence when the tablet is placed in the mouth of a patient (p 4. lines 4-8). Further, such dosage forms are particularly useful in administration of medications to patients who cannot or will not chew, such as children and the elderly (p. 4, lines 9-25).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify oral transmucosyl fentanyl citrate dosage forms of Norling such that to employ the amount of disintegration agents of the instantly claimed . One having ordinary skill in the art would have been motivated to do this to obtain even faster dissolution as well as masking the objectionable flavor of medicaments and providing pleasant organoleptic sensation and as a useful medication

to patients who cannot or will not chew, such as children and the elderly as suggested by Wehling et al. Wehling et al. suggest that the amount of either acid or carbonate source may exceed the amount of the other component in order to enhance taste and/or performance of a tablet containing an overage of either component. With respect to Claims 93 and 94, which recite tablet "adapted for" gingival and sublingual administration, respectively, these types of administration are obvious variations of oral transmucosal administration. Therefore, Claims 93 and 94 don't recite any additional ingredients and/or characteristics, therefore, the combination of references discussed above meets the claimed limitations.

Claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93, 94 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. ('Studies on formulations of fentanyl buccal adhesive tablets", Zhongguo Yiyao Gongye Zazhi, 1997, 28(3), 129-1311) in view of Wehling et al. (WO 91104757) and further in view of Streisand et al. ("Buccal absorption of fentanyl is pH-dependent in dogs', Anesthesiology, (1995 Mar), 82 (3), pp. 759-64).

Chen et al. teach fentanyl citrate buccal adhesive tablets (see Abstract). Chen et al. do not teach the effervescent couple of the instant claims.

Wehling et al. teach effervescent dosage forms for direct oral administration as discussed above.

Streisand et al. teach that the buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic as discussed above.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the adhesive buccal fentanyl tablets of Chen et al. such that to employ effervescent disintegration agents. One having ordinary skill in the art would have been motivated to do this to obtain even faster dissolution as well as masking the objectionable flavor of medicaments and providing pleasant organoleptic sensation as suggested by Wehling et al. Further, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of Wehling et al. such as to employ the excess of the carbonate source (base). One having ordinary skill in the art would have been motivated to do this to obtain basic pH as which the buccal absorption, bioavailability and permeability of fentanyl increase, thus making the tablet more effective, as suggested by Streisand et al. With respect to Claims 93 and 94, which recite tablet "adapted for" gingival and sublingual administration, respectively, these types of administration are obvious variations of oral transmucosal administration. Therefore, Claims 93 and 94 don't recite any additional ingredients and/or characteristics; therefore, the combination of references discussed above meets the claimed limitations.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been fully considered. However it is deemed that the McCarty does not reach the level of a teaching away from the use of conventional disintegrants in buccal dosage forms as suggested by Applicant. A prior art reference that "teaches away" from the claimed

invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.). Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP 2145. The McCarty reference merely teaches that buccal formulations utilize a disintegrant to accelerate buccal tablet disintegration and such disintegrants include polyvinylpyrrolidone, starch, alginic acid, formaldehyde, calcium carboxymethyl cellulose, sodium starch glycolate, and sodium carboxymethyl cellulose etc. The reference does not teach away of using such disintegrants in buccal formulation and therefore it is not a teaching away.

Applicants' argue that McCarty teaches buccal tablets and Wehling teaches tablets to be swallowed. In response, Wehling teaches a formulation that is particularly useful for providing a medicine to those who cannot or will not swallow a tablet (see Abstract). Hence Wehling teaches a dosage form for direct insertion into the mouth of the patient that includes a mixture incorporating water and/or saliva activated effervescent disintegration agent and an effective amount of at least one systematically distributable ingredient (p 3, lines 33-37). Applicants' argue that McCarty recognized buccally absorbable and Wehling never intended to dissolve in the mouth. In response, Wehling teach a tablet that is substantially completely disintegrable upon exposure to water ad/or saliva. The reference further teaches that once the tablet is placed in the patient's mouth it will disintegrate rapidly and substantially completely without any voluntary action by the patient. (p 4, lines 1-15). Applicants' argue that rather than providing a formulation which "rapidly delivers the active ingredient through the buccal route" and requires dissolution of the active in the mouth as desired by McCarty, the use of Wehling would not have been considered for combination as it clearly attempts to prevent in-mouth exposure of the active. In response, Wehling clearly teaches that the systemically distributable ingredient is thus carried into solution or suspension in the patient's own saliva, which the patient ordinarily swallows and even if the patient does not chew the tablet the disintegration will proceed rapidly and teach dosage forms to individuals who cannot or will not chew, patients who have difficulty in swallowing and the elderly. The reference clearly teaches tablets comprising effervescent disintegration

agent providing controlled and rapid disintegration of the tablet when placed in the mouth (p 4-5).

Applicants' argue that McCarty teaches away from using conventional disintegrants and Wehling teaches tablets to be swallowed and the combination of references does not teach the instant invention. In response, McCarty teach fentanyl, an analgesic in buccal formulation and teaches the conventional disintegrants in the background but does not teach away from using such disintegrants. As stated earlier, the prior art's mere disclosure of other alternative does not constitute a teaching away from any of other alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution of using conventional disintegrants. Wehling et al. teach effervescent dosage forms for direct oral administration (i.e. for direct insertion into the mouth of a patient), which comprise at least one systemically distributable ingredient (e.g. a drug), 5 to about 50 % effervescent disintegration agents (a soluble acid source and a carbonate source) and adjuvants such as binders, flavors, colors, fillers, non-effervescent disintegrants, etc. One of ordinary skill in the art would have been motivated to formulate tablets comprising fentanyl and conventional disintegrants to provide faster dissolution of the tablet and also to provide medications to individuals who cannot or will not chew, such as debilitated patients, patients who have difficulty swallowing solids, and the elderly. As stated above, Streisand et al. teach that the buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a

tablet comprising fentanyl, effervescent couple and a pH adjusting substance from the combined teachings of McCarty, Wehling and Streisand.

Applicants' argue that the amount of non-effervescent disintegrants used is up to about 20% in the instant application and McCarty teaches the use of between 90 and about 99% of its sugar. In response, McCarty teach starch as one of the conventional disintegrant and Wehling is used to teach the effervescent couple of the instant claims and the reference teach 20 % of the non-effervescent disintegrants in the effervescent dosage forms comprising a drug such as an analgesic. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to use 20% of the non-effervescent disintegrant in a formulation comprising fentanyl, effervescent couple because of the teachings of Wehling. One of ordinary skill in the art would have been motivated to use such amounts of non-effervescent disintegrants in the composition because of expectation of success as Wehling teaches such amounts in an effervescent dosage form comprising a drug such as analgesic and effervescent couple.

Applicants' argue that Chen reference suffers from many of the deficiencies and does not teach an effervescent couple and a pH adjusting substance. In response, Chen et al. teach fentanyl citrate buccal adhesive tablets and Wehling et al. teach effervescent dosage forms for direct oral administration and Streisand et al. teach that the buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the adhesive buccal fentanyl tablets of Chen et al. such

that to employ effervescent disintegration agents. One having ordinary skill in the art would have been motivated to do this to obtain even faster dissolution as well as masking the objectionable flavor of medicaments and providing pleasant organoleptic sensation as suggested by Wehling et al. One having ordinary skill in the art would have been motivated to obtain basic pH as which the buccal absorption, bioavailability and permeability of fentanyl increase, thus making the tablet more effective, as suggested by Streisand et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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